UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/807,132 | 04/06/2001 | Masatsugu Maeda | 06501-075001 | 4285 |

26161 7590 08/21/2003

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

| EXAMINER | |
|---|---|
| WEGERT, SANDRA L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | 12 |

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/807,132 | MAEDA ET AL. | |
| | Examiner | Art Unit | |
| | Sandra Wegert | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 May 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-12* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

***Status of Application, Amendments, and/or Claims***

The Information Disclosure Statement, submitted 14 February 2002, has been entered into the record as Paper 3. Applicant's election with traverse of Invention I, (claims 1-7 and 12, as pertaining to SEQ ID NO: 4) in Paper No. 11 (4 June 2003) is acknowledged. The Applicant traversed the restriction, arguing that a technical relationship exists between and among the inventive groups and that the polypeptides disclosed share common properties. However, Claims reciting distinct SEQ ID NO's were properly restricted because the sequence in each group provides the special technical feature of that group. The examiner does agree, however, that each of Inventions 1-11 encompass one method of making the product and one method of using the product. Therefore Invention I encompasses claims 8 and 9 as well as claims 1-7 and 12, and will be examined accordingly.

Claims 10 and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected Invention, there being no allowable generic or linking claim.

Claims 1-9 and 12, as reading on SEQ ID NO: 4, are under examination in the current application.

***Specification***

The disclosure is objected to because of the following informalities:

***Title***

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "HUMAN GTAR G PROTEIN-COUPLED RECEPTOR".

Appropriate correction is required.

***Sequence Rules***

The instant application is not fully in compliance with the sequence rules, 37 CFR 1.821-1.825, because each disclosure of a sequence embraced by the definitions set forth in the rules is not accompanied by the required reference to the relevant sequence identifier (i.e., SEQ ID NO:). This happens in Figures 1-6, 10-19 and 24-31.

Appropriate correction is required.

## Claim Rejections/Objections

**Claim Objections**

Claims 1 and 12 are objected to for reciting non-elected subject matter (SEQ ID NO: 5, 6, 28, 29, 30 and 31, for example).

Appropriate correction is required.

***Claim Rejections - 35 USC § 101- non-statutory***

35 U.S.C. 101 reads as follows:

**Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.**

Claims 1, 4 and 12 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims read on a product of nature in that the claimed polypeptide is not isolated or modified. Amending the claims to read "isolated" or "recombinant", for example, would be remedial.

***Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph***

The following is a quotation of 35 U.S.C. 101:

**Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

**The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-6 and 12 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible, specific and substantial asserted utility or a well-established utility.

The claims are directed to the peptide of SEQ ID NO: 4, functional fragments of SEQ ID NO: 4, nucleic acids and vectors encoding SEQ ID NO: 4, and recombinant expression of the peptide of SEQ ID NO: 4.

No well-established utility exists for newly isolated, complex biological molecules. However, the specification asserts the following as credible, specific and substantial patentable

utilities for the disclosed polypeptide and the claimed polynucleotides and recombinant methods used to express it.

1) To search for ligands of the polypeptide of SEQ ID NO: 4,

2) To use drugs for the treatment or prevention of a deficiency in the polypeptide of SEQ ID NO: 4.

3) For the production of antibodies,

4) For gene therapy.

5) To produce a variant or chimeric nucleotide or polypeptide,

6) In the creation of transgenic animals,

7) For use as a G protein-coupled receptor.

Each of these shall be addressed in turn:

*1) To search for ligands of the polypeptide of SEQ ID NO: 4.* This asserted utility is credible. However, it is not substantial or specific. The specification does not characterize the polypeptide encoded by the polynucleotide of the claimed invention. Therefore binding sites, etc. are not identified. Significant further experimentation would be required of the skilled artisan to characterize the protein and search for ligands. There is no disclosure for example, of how to assay for ligand binding and subsequent transduction events or mechanisms. It is not known the class of drugs or small molecules to use or what measurements to perform. Since this asserted utility is not presented in mature form so it could be readily used in a real world sense, the asserted utility is not substantial.

*2) To use drugs for the treatment or prevention of a deficiency in the polypeptide of SEQ ID NO: 4.* This asserted utility is credible and specific, however, it is not substantial. The

specification does not disclose any conditions wherein there is a deficiency of the claimed polypeptide. Significant further experimentation would be required of the skilled artisan to identify individuals who would benefit from such a drug, and then to determine a best course of treatment. There is no disclosure, for example, of dosages or of how to assay for improvement or intolerable levels of side effects, etc. Since this asserted utility is not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

*3) For the production of antibodies.* This asserted utility is credible, but not specific or substantial. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, both the polypeptide and its antibodies have no patentable utility.

*4) For gene therapy.* This asserted utility is credible but not specific or substantial. Such can be performed for any polynucleotide. Thus the asserted utility is not specific. Furthermore, the specification does not disclose diseases associated with a mutated, deleted, or translocated gene of the claimed invention. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease and to determine the route of administration of the gene, as well as quantity and duration of treatment. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

*5) To produce a variant or chimeric nucleotide or polypeptide.* This asserted utility is credible but not substantial or specific. Such manipulations can be done with any polynucleotide. Further, the specification discloses nothing specific or substantial for the variant nucleotide and polypeptide that is produced by this method. Since this asserted utility is also not

present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

*6) In the creation of transgenic animals.* This asserted utility is credible but not specific or substantial. The specification does not disclose a phenotype associated with a mutated, deleted, or translocated gene of the present invention. Significant further experimentation would be required of the skilled artisan to identify such a phenotype. The specification discloses nothing about whether the claimed gene will be "knocked in" or "knocked out" or what specific tissues and cells are being targeted. Since this asserted utility is not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

*7) For use as a G protein-coupled receptor.* This asserted utility is credible, but not specific or substantial. Members of this very large family of proteins share several recognizable structural similarities, yet have diverse functions (see, for example: Ji, et al, 1998, J. Biol. Chem., 273(28): 17299-17302). Furthermore, homology to a class of proteins does not itself confer a specific or substantial function (as discussed below). The specification does not disclose ligands for the receptor, specific transduction steps, its physiological role in the organism, or a link between the receptor and a specific condition or disease state. Determination of any of these would require significant further research. Since the asserted utility is not available as a real world use, and significant further research beyond the disclosure is required, the asserted utility is not substantial.

Claims 1-9 and 12 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or

a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-9 and 12 are directed to the peptide of SEQ ID NO: 4, functional fragments of SEQ ID NO: 4, nucleic acids and vectors encoding SEQ ID NO: 4, and recombinant expression of the peptide of SEQ ID NO: 4.

The specification teaches the polypeptide of SEQ ID NO: 4 and the polynucleotide encoding it. However, the specification does not teach functional or structural characteristics of the polynucleotide or SEQ ID NO: 4 recited in the claims.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a

common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologues must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polypeptides and polynucleotides to make a biologically active G protein-coupled receptor without resorting to undue experimentation to determine what the specific biological activities of the polypeptide are.

The specification does not teach the skilled artisan how to use the claimed polypeptides and polynucleotides *any* purpose. For example, there is no disclosure of particular disease states correlating to an alteration in levels or forms of the polypeptide such that the claimed polypeptides and polynucleotides could be used as a diagnostic tool. Nor are there specific transduction steps given. The skilled artisan is not provided with sufficient guidance to use the claimed polynucleotides for any purpose.

Due to the large quantity of experimentation necessary to determine an activity or property of the disclosed polypeptide such that it can be determined how to use the claimed

polynucleotides and polypeptides and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the unpredictability of the effects of substitution or mutation on protein structure and function, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Furthermore, the specification does not reasonably provide enablement for all *fragments and variants* of SEQ ID NO: 4. The disclosure does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification discloses a DNA of SEQ ID NO: 3 and the peptide of SEQ ID NO: 4. Claims 1 and 3 recite, respectively, polypeptides in which one to thirty amino acids of the protein are modified or deleted, or in which a fragment of unspecified length is recited. However, the specific activities of the protein of SEQ ID NO: 4, and assays to test for its activity, are not disclosed. There is no discussion, or working examples disclosed in the instant case, as to what amino acids are necessary to maintain the functional characteristics of the claimed polynucleotides and polypeptides. The instant case claims altering as much as 10% of the claimed polypeptide in defined ways, and, in the case of Claim 3, altering potentially much more of the polypeptide to get a functional fragment. However, the art shows that receptor families have members with high structural similarities but disparate functions. For example, Smith et al.

(1997, Nature Biotechnology 15:1222-1223) demonstrate that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Therefore, it is not predictable as to which amino acids are necessary to maintain the functional characteristics of a protein.

Due to the large quantity of experimentation required to determine how to use the variants of SEQ ID NO: 4, the lack of direction or guidance in the specification regarding same (e.g., the lack of guidance regarding any specific activity of SEQ ID NO: 4), the lack of working examples to variants of SEQ ID NO: 4, the state of the art showing the unpredictability of function based on structural similarity of homologous proteins, and the breadth of the claims which embrace innumerable variants of SEQ ID NO: 4, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

***Claim Rejections - 35 USC § 112, first paragraph – Written Description.***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1-6 are directed to the peptide of SEQ ID NO: 4, fragments of SEQ ID NO: 4, nucleic acids and vectors encompassing SEQ ID NO: 4.

The specification as originally filed does not provide adequate written description for an isolated protein wherein one to thirty amino acids of the receptor protein are modified or deleted, while still maintaining the function of the receptor. This limitation is not expressly asserted nor does it flow naturally from the specification as originally presented.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The specification as originally filed does not provide adequate written description of the subgenus now claimed. The specification teaches the receptor polypeptide of SEQ ID NO: 4. However, functional assays of the receptor were not performed. The specification does not provide adequate support for a peptide of SEQ ID NO: 4 in which substitutions were made in one to 30 residues, said peptide retaining the function of a G protein-coupled receptor.

Therefore, only a peptide of SEQ ID NO: 4 as disclosed in the Specification, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first

paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Furthermore, Claims 8 and 9 are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 8 and 9 are directed to methods of screening for binding partners or ligands of the peptide of SEQ ID NO: 4.

The specification as originally filed does not provide adequate written description for a method of using a receptor protein with an unknown function to search for specific ligands. This limitation is not expressly asserted nor does it flow naturally from the specification as originally presented.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The specification as originally filed does not provide adequate written description of the method now claimed. The specification teaches the receptor polypeptide of SEQ ID NO: 4. However, functional assays of the receptor were not performed. It is not known what class of ligands to use, what tests to perform, nor what tissues to use, for example. The specification

does not provide adequate support for use of the peptide of SEQ ID NO: 4 in the manner claimed.

Therefore, only a peptide of SEQ ID NO: 4 as disclosed in the Specification, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

***Claim Rejections - 35 USC § 112, second paragraph-indefiniteness.***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

**The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 is rendered indefinite because of the phrase "under highly stringent conditions," which is a conditional term. The metes and bounds of the claim cannot be ascertained. This rejection can be overcome by supplying specific conditions, supported by the specification, which the Applicants consider "stringent."

Conclusion: Claims 1-9 and 12 are rejected for the reasons listed above.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:30 AM to 6:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elyabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

SLW

8/16/03